Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for

Acrylonitrile

ECHA/RAC/ O-0000001412-86-188/F

Adopted

9 March 2018

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR ACRYLONITRILE

Commission request

The Commission, in view of the preparation of the third and fourth proposals for amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD), and in line with the 2017 Commission Communication '*Safer and Healthier Work for All - Modernisation of the EU Occupational Safety and Health Legislation and Policy*'[1], asked the advice of the Committee for Risk Assessment (RAC) to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances.

Therefore, the Commission made a request (8 March 2017[2]) in accordance with Article 77 (3)(c) of the REACH Regulation, to evaluate, in accordance Directive 2004/37/EC, the following chemical compounds: 4,4'-methylenebis[2-chloroaniline] (MOCA), arsenic acid and its inorganic salts, nickel and its compounds, acrylonitrile and benzene.

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission, the Executive Director of ECHA in the mandate of 12 May 2017[3], requested RAC to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for acrylonitrile with a deadline of 26 March 2018.

Chemical name(s): **Acrylonitrile**

EC No.: 203-466-5

CAS No.: 107-13-1

In support of the Commission's request, ECHA prepared a proposal concerning occupational limit values for acrylonitirle at the workplace. This proposal was made

[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes

[2] https://echa.europa.eu/documents/10162/13641/ec_note_to_echa_oels_en.pdf/f72342ef-7361-0d7c-70a1-e77243bdc5c1

[3] https://echa.europa.eu/documents/10162/13641/rac_mandate_for_oels_for_nickel_en.pdf/647788e7-24d2-ff4f-93a0-7d87fdfae28a

publically available[4] on **13 October 2017** and interested parties were invited to submit comments by **10 November 2017**.

RAC developed its opinion on the basis of the proposal submitted by ECHA. During the preparation of the RAC opinion, the ECHA proposal was further developed as a Background Document to ensure alignment. In addition, stakeholders were able to provide comments on the RAC opinion during the evaluation process.

The RAC opinion includes a recommendation to the Advisory Committee on Safety and Health at Work (ACSH) in line with the relevant Occupational Safety and Health legislative procedures and in the format used by SCOEL.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC: **Marja Pronk** and **Sonja Kapelari**

The RAC opinion was adopted by **consensus** on **9 March 2018.**

[4] https://echa.europa.eu/echas-executive-director-requests-to-the-committees-previous-consultations'

RAC Opinion of the assessment of the scientific relevance of OELs for acrylonitrile

RECOMMENDATION

The opinion of RAC for the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for acrylonitrile, is set out in the table below and in the following summary of the evaluation.

SUMMARY TABLE

The table summarises the outcome of the RAC evaluation to derive limit values for the inhalation route and the evaluation for dermal exposure and a skin notation.

Derived Limit Values[5]

OEL as 8-hour TWA:	1 mg/m^3 (0.45 ppm)
STEL (15 min):	4 mg/m^3 (1.8 ppm)
BLV:	60 µg CEV/L blood (erythrocyte fraction of whole blood)[6] (sampling time: after at least 3 months of exposure)
BGV:	Not established

Carcinogenicity Classification

CLP Harmonised classification for carcinogenicity	Carc. 1B: H350
SCOEL Categorisation of carcinogens[7]	Not assigned by SCOEL[8]

Notations

Notations:	'Skin'

[5] The naming conventions of limit values and notations used here follow the 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL 2013; version 7) and the Joint ECHA/RAC – SCOEL Task Force report (2017b). [https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145].

[6] For smokers, an average internal background concentration of about 4 (0.8 to 9.2) µg CEV/L blood has to be considered.

[7] See Appendix 1 of the ECHA Background Document for details on the "SCOEL classification of carcinogens".

[8] In 2003, when SCOEL evaluated acrylonitrile, the scheme was not yet in place

RAC OPINION

Background

This opinion concerns **acrylonitrile** (CAS No. 107-13-1), a colourless, highly volatile liquid with a pungent odour.

The evaluation of acrylonitrile, requested by the Commission, takes into account existing evaluations on the substance, including:

- the recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL, 2003);
- the European Union Risk Assessment Report (EU RAR) (EC, 2004); and
- the evaluation by the International Agency for Research on Cancer (IARC, 1999).

However, in addition to these international reviews, the Background Document prepared by ECHA extensively reviewed more recently published assessments and papers (focussing on health effects and mode of action of carcinogenicity) and of registration dossiers on acrylonitrile provided under the European chemicals legislation REACH[9] (focussing on uses and workers' exposure). Account has also been taken of the comments provided by interested parties during the public consultation.

Key conclusions of the evaluation

- The critical endpoint in establishing the relevance of an OEL for acrylonitrile is its carcinogenicity. From the total weight of evidence from both animal and human data a mode of action-based threshold[10] can be assumed for the carcinogenic effects of acrylonitrile. At acrylonitrile exposures below the resulting proposal for a limit value, no significant residual cancer risk is expected for workers.
- Acrylonitrile has a harmonised classification as Carcinogen 1B under the Classification, Labelling and Packaging Regulation (EC) 1272/2008 (CLP), largely based on animal studies in which acrylonitrile was shown to be a multiple-tissue and multiple-site carcinogen.
- Potentially of most relevance to humans are the brain tumours observed in rats. Rather extensive epidemiology datahowever, do not support a causal association

[9] Regulation (EC) No 1907/2006.

[10] Joint Task Force ECHA Committee for Risk Assessment (RAC) and Scientific Committee on Occupational Exposure Limits (SCOEL) on Scientific aspects and methodologies related to the exposure of chemicals at the workplace. Task 2. 6 December 2017. https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145

between occupational acrylonitrile exposure and increased cancer at a particular site (including the brain).

- Acrylonitrile is genotoxic in vitro and its primary metabolite, 2-cyanoethylene oxide (CEO) appears to be a direct acting mutagen. There is no clear evidence that acrylonitrile is an in vivo mutagen, but the available data are not sufficient to conclude the absence of a mutagenic hazard in all tissues where a carcinogenic response has been seen in animals.
- Although acrylonitrile may have genotoxic potential, and therefore could be considered a genotoxic carcinogen, there is compelling evidence for indirect DNA damage (from oxidative stress) as the main mechanism in rat brain tumour formation. This thresholded mechanism supports a non-linear dose-response relationship, and is further supported by interspecies dose-response comparison analyses of the available animal carcinogenicity data and epidemiology data on acrylonitrile.
- Acrylonitrile is metabolized by two initial pathways: (1) conjugation with glutathione and (2) epoxidation by microsomal cytochrome P-450 forming CEO. The primary metabolites from both pathways are subject to further metabolism, including that of CEO by epoxide hydrolase or conjugation to glutathione to release cyanide.
- Acrylonitrile is acutely toxic and causes neurotoxicity, local irritation of skin, eyes and respiratory tract, and skin sensitisation. Part of this toxicity is due to the metabolism of acrylonitrile to cyanide.
- Acrylonitrile has no effect on reproductive performance or fertility. Developmental toxicity of acrylonitrile is only observed at maternally toxic doses.
- The main route of occupational exposure to acrylonitrile is by inhalation of the vapour.
- Dermal exposure is, however, also possible, as acrylonitrile can readily penetrate the skin. A skin notation is therefore warranted.

Carcinogenicity and mode of action (see ECHA Background Document section 7.7 and 7.10.1 for full discussion)

Acrylonitrile is a multiple tissue site carcinogen in rats following exposure through inhalation, drinking water and gavage. The target organs identified are the central nervous system (CNS; brain and spinal cord), Zymbal's gland, gastrointestinal tract (tongue, forestomach and small intestine) and mammary gland. Astrocytomas in the brain (recently reclassified as malignant microglial tumours) and Zymbal's gland (ear canal) tumours were the most consistent findings, irrespective of the route of administration. Of these two tumours sites, the Zymbal's gland is of less relevance to humans since it has no anatomical human equivalent.

Acrylonitrile is also a multiple tissue-site carcinogen in mice following gavage exposure. In contrast to rats no CNS tumours were observed in mice. Tumours were found in the forestomach and Harderian gland, and (equivocally) in ovary and lung.

There is extensive epidemiology data available on populations occupationally exposed to acrylonitrile (over 26 studies; see ECHA Background Document section 7.7.1 for details). Early studies (pre 1990) suggested a possible increased risk of lung cancer and some other cancer types. However, later studies (including several large, high quality studies using different occupational cohorts in several different countries) and several meta-analyses were not able to confirm a causal association between acrylonitrile exposure in workers and increased cancer at a particular site (including a.o. lung, brain, bladder and prostate). Negative epidemiology data do not allow to reach absolute conclusions that a substance is not a human carcinogen: it is difficult to verify or disprove risk of rare diseases (such as brain tumours) in occupational cohort studies. However, the weight of evidence from good quality epidemiology data on current and past workplace exposures suggests that acrylonitrile is either not a human carcinogen or that it produces only small increases in the risk of cancer.

The observation that the available human epidemiology data is negative whereas the rodent data is positive could point to qualitative differences in sensitivity between rodents and humans (i.e., acrylonitrile is a rodent but possibly not a human carcinogen). The brain tumours, for instance, may be unique to the rat, considering the absence of such tumours in the oral mouse bioassay and the observed absence of excess brain cancer mortality in epidemiology studies.

Alternatively, there may be quantitative differences in kinetics/dynamics or differences in exposure between humans and rodents. PBPK modelling was used to compare lung and brain cancer responses at internal dose levels in humans and animals (Kirman et al., 2005; see ECHA Background Document section 8.1 for details). This allowed to compare cancer mortality from three cohorts of workers exposed to acrylonitrile with exposure-response data from all available rat bioassays. This comparison showed that the past exposures at acrylonitrile workplaces were not orders of magnitude lower than the exposures in the animal studies. Rather, a portion of the worker cohorts were exposed at levels equivalent to those resulting in increased tumour incidences in the rat. This could point to a difference in sensitivity since these occupational exposure levels (with an average of 0.5 ppm, assuming conservatively that the cumulative exposure in the four highest quality cohort studies (about 350,000 ppm-years for approximately 16,000 exposed workers (ECHA Background Document section 7.7.1.4) spread over 40 years) were not associated with increased cancer incidences/mortalities in workers. Yet, neither the number of workers nor the magnitude of the average exposure is high enough to conclude on that with sufficient confidence.

The mode of action (MoA) leading to tumour formation is not fully resolved. There are potentially a variety of ways in which acrylonitrile could induce cancer, given the various tissue sites where it was experimentally seen to have induced tumours in animals. When looking at its genotoxicity profile (see ECHA BACKGROUND DOCUMENT section 7.6 for details), acrylonitrile is genotoxic in vitro and its primary oxidative metabolite, 2-cyanoethylene oxide (CEO), appears to be a direct-acting mutagen. There is no clear

evidence that acrylonitrile is an in vivo mutagen, but the available data are not sufficient to conclude the absence of a mutagenic hazard in all those tissues where a carcinogenic response has been seen in animals.

Acrylonitrile as well as CEO and cyanide are capable of crossing the blood–brain barrier, and possible modes of action by which the brain tumours may have been induced in rats include direct genotoxicity (from CEO), indirect genotoxicity (from oxidative stress) and non-genotoxic mechanisms (via loss of gap junction intercellular communications, but supporting evidence is so far limited to a single in vitro study). All three MoAs are known to occur in humans.

In general, substances that cause tumours at multiple tissue sites most commonly have a DNA-reactive MoA. Further, a number of tissue sites (including the Zymbal's gland, mouse forestomach and Harderian gland) are very response to DNA-reactive carcinogens (Haber and Patterson, 2005). The tumour profile of acrylonitrile (with tumours in a.o. Zymbal's gland, forestomach and Harderian gland) would fit with acrylonitrile being a genotoxic DNA-reactive carcinogen. However, a lack of DNA-adduct formation in rat brain tissue following exposure (in vitro and in vivo) to acrylonitrile (see ECHA BACKGROUND DOCUMENT section 7.6.2.1) does not support a major role for direct genotoxicity.

The evidence suggests, however, that indirect genotoxicity via oxidative stress may play an important role: oxidative DNA damage and reactive oxygen species (ROS) formation have been shown following acrylonitrile exposure in several in vitro and in vivo studies (via oral route) (see ECHA Background Document section 7.6.2.1). The oxidative DNA damage appears to arise mainly through the oxidative pathway (oxidative metabolites CEO and cyanide), with glutathione depletion contributing to the damage. From the in vivo studies using drinking water administration there seems to be a concordance between the acrylonitrile dose levels inducing oxidative stress (≥30 ppm) and those resulting in higher brain tumour incidences in the oral rat bioassays (≥30 ppm), with no such increases at 10-fold lower levels. In the absence of mechanistic studies investigating the (thresholded) oxidative stress MoA following inhalation exposure, it is difficult to draw a conclusion on the importance of this MoA and its temporal and dose concordance with brain tumour induction upon inhalation acrylonitrile exposure. The MoA for the inhalation route is however not expected to differ much from that for the oral route.

In view of the above, the data available for acrylonitrile are considered insufficient to definitively identify a specific key event or unequivocal MoA for the brain tumours induced in rats.

There is no additional information available to inform on possible MoAs of relevance for the other target tissues seen for acrylonitrile carcinogenicity. It cannot be discounted that multiple MoAs may apply, not all of which will be thresholded (i.e. non-linear).

Overall, given that:

- acrylonitrile is a multiple tissue site carcinogen in rats and mice;

- the MoA behind acrylonitrile tumour formation is likely complex and could include multiple mechanisms, not all of which might be non-linear and each of which could predominate at different doses,
- the possibility of an occupational cancer risk cannot totally be excluded, however high quality epidemiology studies do not indicate increased cancer incidences/mortalities in acrylonitrile workers;

RAC considers carcinogenicity to be a critical endpoint for establishing an OEL for acrylonitrile. In doing so, the OEL should also be sufficiently protective for non-cancer effects of acrylonitrile, in particular neurotoxicity and nasal irritation.

Cancer Risk Assessment and Derived Limit Values (see ECHA Background Document section 8 for full discussion)

RAC notes that in most evaluations of acrylonitrile so far (e.g. SCOEL, 2003; EU RAR, 2004; AGS, 2010) the substance has been considered a non-threshold carcinogen, because it was concluded that the available data on acrylonitrile do not allow to conclusively rule out a potential role for direct genotoxicity. For non-threshold carcinogens, dose-response relationships for carcinogenicity are normally derived by linear extrapolation. This has also been done for acrylonitrile in most existing evaluations (see for details ECHA Background Document section 8.2). Extrapolating outside the range of observation however inevitably introduces uncertainties. In the case of acrylonitrile, several modes of action may be behind the tumour formation in rodents, and although the available data do not allow to conclusively rule out a potential role for direct genotoxicity, RAC notes there is more compelling evidence for a major role of oxidative stress in the carcinogenicity. This mechanism suggests non-linearity of the dose-response, as it is thresholded. It is thus expected that linear low-dose extrapolation will significantly overestimate the excess cancer risk. RAC notes that a quantitative comparison of the epidemiology exposure-response data to the rat brain tumour data in terms of internal doses (derived with PBPK modelling) points to sub-linearity and thus to inconsistency with linear low-dose extrapolation for human risks for lung and brain cancer (Kirman et al., 2005; see ECHA Background Document section 8.1 for details).

In weighing all the available evidence, RAC is therefore of the opinion that a mode of action-based threshold for the carcinogenic effects is plausible and that a limit value can be derived for acrylonitrile.

Derivation of limit value (8-hour TWA)

Ideally, the PoD for the limit value would be a NOAEC for the relevant precursor effect, i.e. oxidative stress. Unfortunately, the available data are insufficient (in particular for the inhalation route) to allow determination of a such a NOAEC. That leaves the brain tumour incidence data as PoD. RAC considers the BMDL05 of 60 mg/m^3 (27.6 ppm) the best available PoD, given that it has been determined following BMD-modelling of all male and female brain tumour incidences from all dose levels in all available carcinogenicity studies for acrylonitrile (Kirman et al., 2005; see ECHA Background

Document section 8.1 for details). Making use of all available dose-response information is to be preferred over solely taking the N(L)OAEC from one study (in this case the LOAEC of 20 ppm from the key 2-year inhalation study by Quast et al. (1980)).

By applying a total assessment factor of 62.5 to the BMDL05, RAC derives a limit value of 1 mg/m^3 (rounded; 0.45 ppm). This factor consists of the following subfactors (see ECHA Background Document section 8.1 for details):

- a factor of 2.5 to account for interspecies differences:
    - 2.5 for interspecies toxicodynamic (TD) differences (default, because a potentially higher sensitivity of humans cannot be completely excluded, given that the detection of low risk increases for rare tumours such as of the brain would require extremely high numbers of exposed subjects);
    - 1 for interspecies toxicokinetic (TK) differences (substance-specific, as PBPK-modelling was used for the external-internal dose conversions);
- a factor of 5 to account for intrapecies differences:
    - 2.24 for intraspecies TD differences (assuming equal contributions of the TD and TK factors to the total intraspecies default factor of 5 for workers);
    - 2.2 for intraspecies TK differences (substance-specific, based on variability analysis of the PBPK model used);
- a factor of 5 to account for dose-response and severity.

The latter factor takes into account the fact that the point of departure is a BMDL05. Whereas for non-cancer effects a BMDL05 is generally considered comparable to a NOAEL, for cancer it may be seen as an effect level, given that 5% is a fairly significant response for such a severe effect. Noting however that from the epidemiology data the risk to humans appears low, if any, RAC considers a factor of 5 sufficient.

The limit value derived needs also to be sufficiently protective against non-cancer endpoints. Local irritation and neurological effects are consistent findings in humans and animals following acrylonitrile exposure (see ECHA Background Document sections 7.2-7.4). In adult experimental animals, the most sensitive effects were local irritant effects in the nasal epithelium, with a LOAEC of 20 ppm in the 2-year rat inhalation study by Quast et al. (1980) and a NOAEC of 15 ppm in the more recent 2-generation rat inhalation study by Nemec et al. (2008). The LOAEC in the latter study was 45 ppm. From the (relatively old) human data, levels below 5 ppm following acute exposure do not appear to result in local irritation and neurotoxicity. Following repeated exposure, some subjective effects seem to start around 1-10 ppm and above, but the data are difficult to assess in relation to dose-response and thus not considered sufficiently robust to use as PoD for setting a limit value for the non-cancer effects. Taking therefore as PoD the lowest level effective in causing treatment-related local irritancy in the nasal epithelium (20 ppm), a limit value of 0.7 ppm (rounded; corresponding to 1.5 mg/m^3)

can be derived following conversion of the PoD into a worker equivalent dose and applying assessment factors of 1 for remaining interspecies differences (because the human data do not indicate humans to be more sensitive than rats), 5 for worker intraspecies differences, and 3 for LOAEC-NAEC extrapolation (see ECHA Background Document section 7.9 for details of the derivation).

RAC notes that the limit value of 1 mg/m^3 (0.45 ppm) proposed for cancer effects will also be sufficiently protective against local irritant effects in the nose. RAC further notes that given the proposed limit value, the OELs currently in use in various EU Members States (1–2 ppm) may no longer be appropriate.

Since the proposed limit value assumes a mode of action-based threshold for the carcinogenic effects of acrylonitrile, some uncertainties with regard to residual cancer risk remain (see further also ECHA Background Document section 8.2). However, the level of uncertainty is considered to be low, in view of the evidence that in high quality epidemiology studies a conservatively estimated average exposure of 0.5 ppm is not associated with increased cancer incidences/mortalities in workers.

At the proposed limit value, no measurement difficulties are foreseen (see ECHA Background Document section 6.1 for analytical methods). With current air measurement techniques it is possible to achieve levels at least down to 10% of the proposed limit value.

Background exposure

Industrial and non-industrial sources (as a result of burning nitrogen containing biomass, timber and tobacco) can result in acrylonitrile exposure via ambient air. Concentrations of up to 100 µg/m^3 have been reported in ambient air, but are typically less than 10 µg/m^3, so much lower than the proposed limit value.

Short term exposure limit (STEL)

Acrylonitrile is classified for acute inhalation toxicity in CLP Category 3 (H331: Toxic if inhaled). Signs of acute toxicity have also been reported for humans (see ECHA Background Document section 7.2.1). RAC noted that the manufacture and further processing of acrylonitrile occur in closed or partially closed systems (see ECHA Background Document section 5), but there may be occupational tasks at industrial sites presenting a short term acute exposure risk. So, a STEL may be warranted, allowing the OEL (8-hour TWA) to be exceeded for a maximum of 4x 15 minutes in 8 hours, with an interval of 60 minutes between two peaks.

In setting the STEL for a carcinogenic substance, the dose-time product is in principal a decisive factor since the total exposure over a shift must remain below the 8-hour TWA. It is important that detoxifying metabolic pathways still obey linear kinetics at the concentration peaks. Assuming this is the case for acrylonitrile, given the major role for an indirect MoA via oxidative stress, and given further that the exposure pattern might be considered more continuous than peak-like, a STEL of 4x the 8-hour TWA may be

appropriate. The resulting STEL of 4 mg/m^3 (1.8 ppm) is protective against irritation/neurotoxic effects; limited data available for humans seem to indicate that levels below 5 ppm following acute exposure do not appear to result in local irritation and neurotoxicity (see e.g. Jakubowski et al., 1987 in ECHA Background Document section 7.2.1).

Biological Monitoring (see ECHA Background Document section 6.2 for full discussion)

Possible biomarkers of acrylonitrile exposure and toxicity are N-(2-cyanoethyl)valine (CEV), thiocyanate and cyanide. The most specific biomarker is CEV (Fennell et al., 2000; Colenbie et al., 2017), a protein adduct formed by reaction of acrylonitrile with the N-terminal valine in haemoglobin. The analytical methodology for measurement of CEV in blood (erythrocytes) is extremely sensitive, with a limit of detection (LoD) of about 0.1–1 pmol CEV/g globin (Tavares et al., 1996, Licea Peres et al., 1999), corresponding to 0.0024-0.024 µg CEV/L blood. Given that CEV has a half-life corresponding to half the life-span of erythrocytes (≈ 60 days), sampling needs to be done only after at least 3 months of exposure.

Biological guidance and limit values

For acrylonitrile a correlation has been established between its concentration in air and the biomarker N-(2-Cyanoethyl)valine (CEV) in blood (DGUV, 2016), the so called EKA correlation (Exposure Equivalent for Carcinogens). This correlation is based on measured air concentrations (0.3 mg/m^3 (0.14 ppm), 0.5 mg/m^3 (0.23 ppm), 1 mg/m^3 (0.45 ppm)) and corresponding measured concentrations of CEV in blood. For higher concentrations, the correlation is based on linear extrapolation from the relation found at 1 mg/m^3. As the proposed limit value of 1 mg/m^3 (0.45 ppm) equals one of the concentrations underlying the EKA correlation, RAC considers the corresponding CEV level of 60 µg CEV/L blood (erythrocyte fraction of whole blood) to be an appropriate biological limit value (BLV) (with sampling time after at least 3 months of exposure).

RAC notes that CEV is a marker for long-term exposure and is influenced by other sources of acrylonitrile (e.g. smoking). Background levels in smokers are >50 pmol/g globin (>1.2 µg CEV/L blood). Knowing that around 4 (0.8 to 9.2) µg CEV/L blood or 8.5 fmol/mg globin/cigarette/day (Fennell et al., 2000) could be due to smoking, this can be accounted for when evaluating measured CEV concentration in blood. In non-occupationally exposed non-smokers, the CEV level in blood is <10 pmol/g globin (<0.24 µg CEV/L blood).

Since a BLV can be derived, no biological guidance value (BGV) is recommended. RAC notes that for adult non-smokers the MAK Commission (DFG, 2016) has established a biological reference value (BAR)[11] of 0.3 µg CEV/L blood (erythrocyte fraction of whole blood).

[11] A BAR describes the background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally

Notations

For acrylonitrile it is known that it is readily absorbed after dermal administration and that severe intoxications have been described in persons incidently or accidently exposed to acrylonitrile by skin contact. A skin notation is therefore warranted.

ANNEXES:

Annex 1 The Background Document gives the detailed scientific grounds for the opinion. The Background Document was prepared by the European Chemicals Agency (ECHA).

Annex 2 Comments received on the ECHA proposal, response to comments provided by the ECHA Dossier Submitter and RAC (excluding confidential information).

exposed to this substance. The BAR are based on the 95th percentile without regarding effects on health. It must be taken into account that the reference level of the background exposure can be influenced by such factors as age, sex, social status, residential environment, life style and geographical region.